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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/774,178	02/01/2001	Tetsuya Ishizuka	P66351US0	7485

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JACOBSON HOLMAN PLLC
400 SEVENTH STREET N.W.
SUITE 600
WASHINGTON, DC 20004

EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 04/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/774,178	ISHIZUKA ET AL.	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 February 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/23/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

FINAL ACTION

1. Applicant's amendment filed February 23, 2005 is acknowledged and has been entered. Claims 1-10 have been canceled. Claims 11- 22 have been added. Claims 11-22 are pending. All of the arguments have been thoroughly reviewed and considered but are deemed moot in view of the new grounds of rejections necessitated by Applicant's amendment of the claims. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims.

This action is made FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on February 23, 2005 is acknowledged and has been entered. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner. A signed copy of the form-1449 is attached to this Office Action.

New Ground(s) of Rejections

THE NEW GROUNDS OF REJECTIONS WERE NECESSITATED BY APPLICANT'S AMENDMENT OF THE CLAIMS:

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 11-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 11-22 are indefinite and confusing in claims 11 and 21 for the limitation "wherein the transcribed RNA is the target RNA" because it unclear if reference is being made to the target RNA as indicated in the step (a) as being the same target in the step (b). It is unclear the nexus between the "target RNA" in the step (a) versus the "target RNA" in the step (b). Alternatively, it is unclear if Applicant is referring to a "new target" for another round of amplification. Such steps are not indicated and thus unclear how the "wherein clause" in step (b) further limits or defines the method. Clarification is required.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Note** The "wherein clause" in step (b) of the independent claims 11 and 21 is vague and confusing and thus it cannot be determine how the "wherein limitation" further limits are define the instant invention. Therefore, for the purpose of application of prior art, the step (b) to (c) is being interpreted as "repeating the steps using the transcribed RNA".

8. Claim 11, 12, 17, 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakahara et al (Nucleic acids Research, Vol. 26, No. 7, pages 1854-1855, April 1998) in view of Kievits et al (5, 654,142, August 5, 1997). Regarding claim 11, Nakahara et al teach a method of amplifying a target RNA comprising the steps of producing double stranded DNA having a promoter sequence by using the target RNA as a template, (b) transcribing the double stranded DNA in a reaction solution in the presence of an RNA polymerase from phage T7 and ribonucleotide triphosphates, wherein the ribonucleotide triphosphates include: adenosine triphosphate (ATP), uridine triphosphate (UTP), cytidine triphosphate (CTP) and guanosine triphosphate (GTP) at a final concentration of 2mM and inosine triphosphate (ITP) at a final concentration of 0 to 4mM to produce transcribed RNA and detecting the product formed therein (see entire reference, especially page 1855, col. 1, Figure 1 legend). Nakahara et al differs from the instant invention in that the reference does not teach the repeating the steps using the transcribed RNA.

In a method similar to that of Nakahara et al, Kievits et al teach amplifying a target RNA containing a specific base sequence in a sample by an RNA amplification procedure which comprises a step of forming a double-stranded DNA which has a promoter sequence and is capable of transcribing into an RNA comprising a specific base sequence, a step of forming an RNA transcript comprising the specific base sequence using an RNA polymerase and a step of forming a double stranded DNA using the RNA transcript as the template, in the presence of

adenosine triphosphate (ATP), guanosine triphosphate (GTP), cytosine triphosphate (CTP), uridine triphosphate (UTP) and inosine triphosphate (ITP) as substrates of the RNA polymerase. Kievits et al further teach wherein the transcribed RNA may act as a template for subsequent generation of double stranded DNA template comprising a promoter (col. 3, line 49 to col. 4, line 7, col. 5, line 8 to col. 6, line 29). Therefore, in view of the teaching of Kievits et al, it would have been obvious to one of ordinary skill in the art at the time of the claimed invention that the RNA of Nakahara et al may act as a template for subsequent generation of double stranded DNA template comprising a promoter with a reasonable expectation of success as taught by Kievits et al.

Regarding claim 12, Nakahara et al teach the method according to claim 11, wherein the ratio of the final concentration of ITP to the rNTP is from 0.5:1.0 to 1:1 (see page 1855, Figure 1 legend).

Regarding claim 17, Nakahara et al teach a method according to claim 11, wherein the transcribing step further occurs in the presence of: -a primer complementary to the base sequence of the target RNA and a primer homologous to the base sequence of the target RNA, wherein either the primer complementary to the base sequence of the target RNA or the primer homologous to the base sequence of the target RNA has at it's 5' end a promoter sequence for the RNA polymerase from phage T7 (page 1855, Figure 1 legend).

Regarding claim 18, Kievits et al teach the method of claim 17, wherein the step of forming double stranded DNA by: reverse transcribing the target RNA with RNA-dependent DNA polymerase to produce single-stranded DNA and reverse transcribing the single stranded

DNA with DNA -dependent DNA polymerase to produce double stranded DNA (col. 6, lines 14-30).

Claim Rejections - 35 USC § 103

9. Claim 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakahara et al in view of Kievits et al as previously applied above and further in view Sheldon III et al (US 4,582,789 April 1986). Regarding claims 19 and 20, Kievits et al teach a method of amplifying a target RNA as previously discussed above. Kievits et al further teach wherein the method may be carried out in the presence of a probe comprising a label (col. 3, line 49 to col. 4, line 14).

Nakahara et al in view of Kievits et al differ from the instant invention in that they do not teach wherein the probe is labeled with a fluorescent intercalative dye and monitoring the fluorescence intensity of the reaction solution. The references also do not teach wherein the fluorescent intercalative dye alters its fluorescence upon hybridization with the transcribed RNA. Sheldon III et al provides a general teaching of labeling nucleic acids, preferably probes, with an intercalation moiety (dye) capable of altering its fluorescence property for use in hybridization assay for detecting nucleic acids (col. 6, lines 5-27, lines 43-68; col. 17, lines 3-41; col. 20, lines 33-50). Sheldon III et al teach that the labeled probed comprising an intercalative moiety is useful in application for detecting nucleic acid sequences (RNA/ and or DNA) such as e.g., those characteristic of a pathogenic microbe or those responsible for or linked to a genetic disease (col. 17, lines 3-7). Therefore, in view of the foregoing, one of ordinary skill in the art at the time of the claimed invention would have been motivated to have encompassed an intercalative moiety

to the probe as taught by Kievits et al in the method of amplifying RNA as taught by Nakahara et al and Kievits et al for the advantages of detecting nucleic acid sequence (RNA sequences) characteristics responsible for or linked to a genetic disease as suggested by Sheldon III et al.

Applicant's traversal

10. Applicant traverses the rejection of Nakahara et al and Kievits et al on the following grounds: Applicant states that Kievits et al discloses that "Good results are obtained when nor more than 50% of the GTP present in an amplification reaction mixture is substituted with ITP and the optimal ratio of ITP:GTTP has been found to be approximately 1:3". Applicant states that Kievits teaches away from the presently claimed invention. Applicant state that Nakahara et al discloses that "an increase in the yield of NASMA products was observed at peaking at 1.5 to 2mM and that "The optimal ITP concentration was determined to be 2mM". Applicant concludes that Nakahara does not teach the presently claimed invention. Applicant further states that the secondary references, such as Sheldon III et al does not cure the deficiencies found in Nakahara et al and Kievits et al. Therefore, Applicant asserts that the rejections should be withdrawn.

Examiner's Response

11. In response to Applicant arguments that the Kievits teaches away from the instant invention by teaching a ratio of ITP:GTP as being approximately 1:3, it is noted that a ratio of ITP to GTP falls with the recommend range of the instant invention because the reference teaches wherein the ITP to rNTP is from 05:1 to 0.5:10. Thus a ratio of 1:3 as taught by Kievits is encompassed by the instant invention. In regards to Applicant's arguments that the reference of Nakahara et al do not disclosed the instant invention, it is noted that the reference of Nakahara

et al teach concentrations of ITP from 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5 and 4mM (see figure 1 legend), which falls within the required ranges of concentration of ITP as required by the claims. Applicant's arguments are not sufficient to overcome the prior art teachings of Nakahara et al and Kievits et al.

Claim Rejections - 35 USC § 103

Note* The preceding rejections are based on Applicant's submission of an information disclosure statement after the first Action on the merit.

12. Claims 13-16, 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leone et al (Nucleic acids Research 1998, vol. 26, no. 9, pages 2150-55 (ref cited on IDS) in view of Malek et al (Methods in Molecular Biology, 1994, vol. 38, pages 253-60). Regarding claims 13-16, 19-22, Leone et al teach a method of amplifying a target RNA comprising the steps of producing double stranded DNA having a promoter sequence by using the target RNA as a template, (b) transcribing the double stranded DNA in a reaction solution in the presence of an RNA polymerase from phage T7 and ribonucleotide triphosphates, wherein the ribonucleotide triphosphates include: adenosine triphosphate (ATP), uridine triphosphate (UTP), cytidine triphosphate (CTP) and guanosine triphosphate (GTP) at a concentration of 5mM to 10mM and inosine triphosphate (ITP) at a concentration of 2.5 mM to produce transcribed RNA and repeating the steps using the transcribed RNA as the template (page 2151, section entitled "Material and Methods", col. 1 to first paragraph of col. 2). Leone further teach wherein the method is performed in the presence of a fluorescently labeled probe that hybridizes with the transcribed RNA and monitoring the fluorescence of the reaction solution wherein the fluorescently labeled probe alters upon hybridization of the probe with the transcribed RNA

(page 2151, col. 1, section entitled "Materials and Methods" and page 2152-2153, section entitled "Results").

Leone et al differs from the instant invention in that the reference does not teach wherein the concentration of rNTPs is 3.5 mM to 5.0 mM and the concentration of inosine triphosphate is 1.0 mM to 2.7 mM. The reference also does not teach wherein the tris-HCl buffer has a concentration of 50mM to 80mM or 20. 50 mM. However, Leone et al do teach vary concentrations of reagents to optimize RNA detection conditions.

Malek et al provides a general teaching of an RNA amplification method similar to that of Leone for detecting target RNA molecules. Malek et al provides tips and conditions for preparing and using reagents required in the RNA amplification method. Malek et al teach preparation of stock solutions of rNTPs, NTPs and buffer solutions for use in the RNA amplification reaction. Malek et al teach that a 1M stock of Tris-HCL and Magnesium chloride should be prepared for use in the RNA amplification reaction. Malek et al teach that a 25 mM stock of dNTPs and NTP should be prepared for use in the RNA amplification reaction (see page 254-256). Malek et al teach that these stocks can be diluted to obtain varying concentration to optimize the conditions of the RNA detection (page 257; see also page 258 to 259). Therefore, given the teaching of Malek et al for stock preparation of reagents necessary for the RNA amplification reaction and dilution conditions, one of ordinary skill in the art at the time of the claimed invention would have been motivated to modify or vary the concentrations of reagents required for the RNA amplification reaction of Leone et al by e.g., dilution, to optimize the RNA detection conditions as suggested by both Leone et al and Malek et al. Additionally, the optimal concentrations are based on the practitioner's desired results as taught by Malek et al.

Conclusion

13. No claims are allowed. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

4/25/05